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## Cytomegalovirus in inflammatory bowel disease: A systematic review

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### Abstract

**AIM:** To identify definitions of cytomegalovirus (CMV) infection and intestinal disease, in inflammatory bowel disease (IBD), to determine the prevalence associated with these definitions.

**METHODS:** We conducted a systematic review and interrogated PubMed, EMBASE and Cochrane for literature on prevalence and diagnostics of CMV infection and intestinal disease in IBD patients. As medical headings we used "cytomegalovirus" OR "CMV" OR "cytomegalo virus" AND "inflammatory bowel disease" OR "IBD" OR "ulcerative colitis" OR "colitis ulcerosa" OR "Crohn's disease". Both MeSH-terms and free searches were performed. We included all types of English-language (clinical) trials concerning diagnostics and prevalence of CMV in IBD.

**RESULTS:** The search strategy identified 924 citations, and 52 articles were eligible for inclusion. We identified 21 different definitions for CMV infection, 8 definitions for CMV intestinal disease and 3 definitions for CMV reactivation. Prevalence numbers depend on used definition, studied population and region. The highest prevalence for CMV infection was found when using positive serum PCR as a definition, whereas for CMV intestinal disease this applies to the use of tissue PCR > 10 copies/mg tissue. Most patients with CMV infection and intestinal disease had steroid refractory disease and came from East Asia.

**CONCLUSION:** We detected multiple different definitions used for CMV infection and intestinal disease in IBD patients, which has an effect on prevalence numbers and eventually on outcome in different trials.

**Key words:** Inflammatory bowel disease; Cytomegalovirus; Ulcerative colitis; Crohn's disease; Systematic review

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**Core tip:** The use of different definitions for cytomegalovirus (CMV) infection and CMV intestinal disease in inflammatory bowel disease (IBD) patients has great impact on the reported prevalence rates (definitions with highest prevalence: positive serum PCR (CMV infection) and tissue PCR > 10 copies/mg tissue (CMV intestinal disease)). In addition, prevalence rates depend on the studied population (highest prevalence: steroid refractory disease), and region (highest prevalence: East Asia). Our key message is not to develop more sensitive diagnostics to find CMV, but to organise a global consensus meeting on CMV in IBD to formulate one unified definition for clinically relevant CMV (intestinal) disease in IBD.

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## INTRODUCTION

Cytomegalovirus (CMV) is a member of human herpesvirus family<sup>[1]</sup>. CMV infection is common and mostly asymptomatic in healthy people. Seroprevalence data differ depending on the healthcare circumstances or immunocompetency of the host, but most studies give a seroprevalence of 40%-100% in adults<sup>[2-4]</sup>, with the highest prevalence in non-western countries<sup>[5,6]</sup>. In immunocompromised patients CMV infection may follow a complicated course resulting in retinitis, pneumonia and intestinal disease (mostly colitis) or other organ specific disease<sup>[7-9]</sup>. The role of cytomegalovirus (CMV) in inflammatory bowel disease (IBD) is under scrutiny. Here, the discussion mainly focuses on either the association or causation of CMV infection and intestinal disease in adverse outcomes in IBD patients. The applied definitions for both CMV infection and CMV intestinal disease, are crucial in this issue, and the answer to the above key question can only be given when there is a unified gold standard definition of clinical relevant CMV infection and intestinal disease, which is lacking at this moment. Our aim was to perform a systematic review of the literature to identify the different definitions for CMV infection and intestinal disease in IBD patients, and to connect the used definitions to the reported prevalence. In addition we summarize the different diagnostic strategies for CMV infection and intestinal disease.

## MATERIALS AND METHODS

### Search strategy and study selection

A search of the medical literature was conducted using MEDLINE, EMBASE and the Cochrane central register

of controlled trials, until December 2014, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>[10,11]</sup>. The study was registered in the PROSPERO database registry (PROSPERO registration number CRD 42015017451). The search strategy was designed to identify English-language (clinical) trials concerning diagnostics and prevalence of CMV in IBD. The following medical search headings were used: "cytomegalovirus" OR "CMV" OR "cytomegalo virus" AND "Inflammatory Bowel Disease" OR "IBD" OR "ulcerative colitis" OR "colitis ulcerosa" OR "Crohn's Disease". Both MeSH-terms and free searches were performed. Studies were eligible if they reported on prevalence and/or diagnostic criteria to define CMV infection or CMV intestinal disease in IBD (Table 1).

Because of the paucity of prospective, randomized, controlled trials on this subject, we aimed to consider all types of evidence available. To this end, we also included observational studies, case-control studies and retrospective studies. We excluded non-English literature, case reports, case series with  $n < 10$  cases and review articles. We also excluded studies that concerned CMV and pouchitis, or studies that concerned the causative relationship of CMV and IBD.

Two independent reviewers (Römkens TEH, Bulte GJ) performed the first selection, and screened title and abstract of the papers identified by electronic search. They completed an inclusion form for eligible studies. Additional articles were obtained through citation snowballing to locate primary sources. When no abstract was available, the article was always screened by full text. Three investigators read all full text papers, and disagreements were resolved by consensus (Römkens TEH, Bulte GJ and Nissen LHC).

### Outcome assessment

The primary outcomes were: (1) a list with all used definitions of CMV infection or CMV intestinal disease in IBD patients; and (2) prevalence numbers to assess the effect that the applied definition has on the reported prevalence of CMV in IBD patients. Secondary outcomes were: (1) prevalence of CMV in subpopulations as ulcerative colitis (UC), Crohn's disease (CD), steroid refractory disease; and (2) prevalence of CMV in different regions of the world. We also summarized different diagnostic strategies for CMV infection in IBD patients.

### Data extraction and assessment of risk of bias

The data extraction process was carried out using a pre-established protocol. Full papers were reviewed using a purpose-designed database. The following clinical data were extracted for each trial: single- or multicenter, country of origin, duration of follow up, study period, sample size, characteristics of the studied population, medication at baseline, used diagnostics for CMV infection, criteria used to define CMV infection, criteria used to define CMV intestinal disease, CMV

**Table 1** Eligibility criteria for inclusion

Adults
Diagnosis of IBD, according to international guidelines
English language
Prevalence and/or diagnostics CMV infection or intestinal disease reported
Minimal sample size 10 patients

IBD: Inflammatory bowel disease; CMV: Cytomegalovirus.

prevalence and authors conclusion. Assessment of risk of bias was performed independently by three investigators, with disagreements resolved by discussion. Risk of bias was assessed by recording of study type, retrospective or prospective design, sample size, study period and follow up, whether or not randomization or blinding was used, and recording specific population characteristics that pose a risk for selection bias (type and severity of IBD, medication use, exclusion criteria).

### Statistical analysis

All abstracted data were entered into a structured database. We displayed the results for both CMV infection and intestinal disease in IBD patients separately, in line with the fact that these are two different entities. In addition to detailed tables, we provide the main results in scatterplots in order to give more insight in sample size, median and range of the various definitions. Next to this, we provide scatterplots of prevalence by definition in different subgroups as UC, CD, steroid refractory IBD, and IBD patients in different regions of the world. Kappa statistics were used to analyze agreement among the reviewers. Evidence-tables were provided for all characteristics of the included studies. We could not carry out a meta-analysis because head-to-head comparison of the included studies was impossible due to heterogeneity.

## RESULTS

### Selected studies

Our search strategy generated a total of 924 citations, of which 190 (168 + 22) published articles appeared to be relevant, and were retrieved for further assessment (Figure 1). Of these, 138 (118 + 20) articles were excluded for various reasons, leaving 52 eligible articles. The main reasons for exclusion were case reports; reviews; non-IBD patients; no information on CMV (intestinal) infection and non-English literature. Agreement in this step between reviewers was 88% (Cohen's Kappa 0.73) before consensus meeting. Study (risk of bias) variables are shown in Appendix 1. Most of the included studies have small sample sizes. None of the included studies was randomized and most of the study designs were single centre ( $n = 42/50$ ) with more than half of them using a retrospective

design (26/48). Some used blinding for the reviewing pathologist (6/43) or endoscopist (2/43).

### Definitions and prevalence

We identified 21 different definitions for CMV infection, and 8 definitions for CMV intestinal disease (Tables 2 and 3). Three definitions for reactivation of CMV are listed in Table 4. Some studies do not mention or define CMV infection, but report prevalence numbers of "mucosal expression"<sup>[12]</sup>, or "presence of CMV"<sup>[13,14]</sup> and some provide a prevalence rate without defining CMV infection<sup>[15-62]</sup>.

Prevalence data for definitions used more than once for respectively CMV infection and intestinal disease are listed in a scatter plot (Figures 2 and 3).

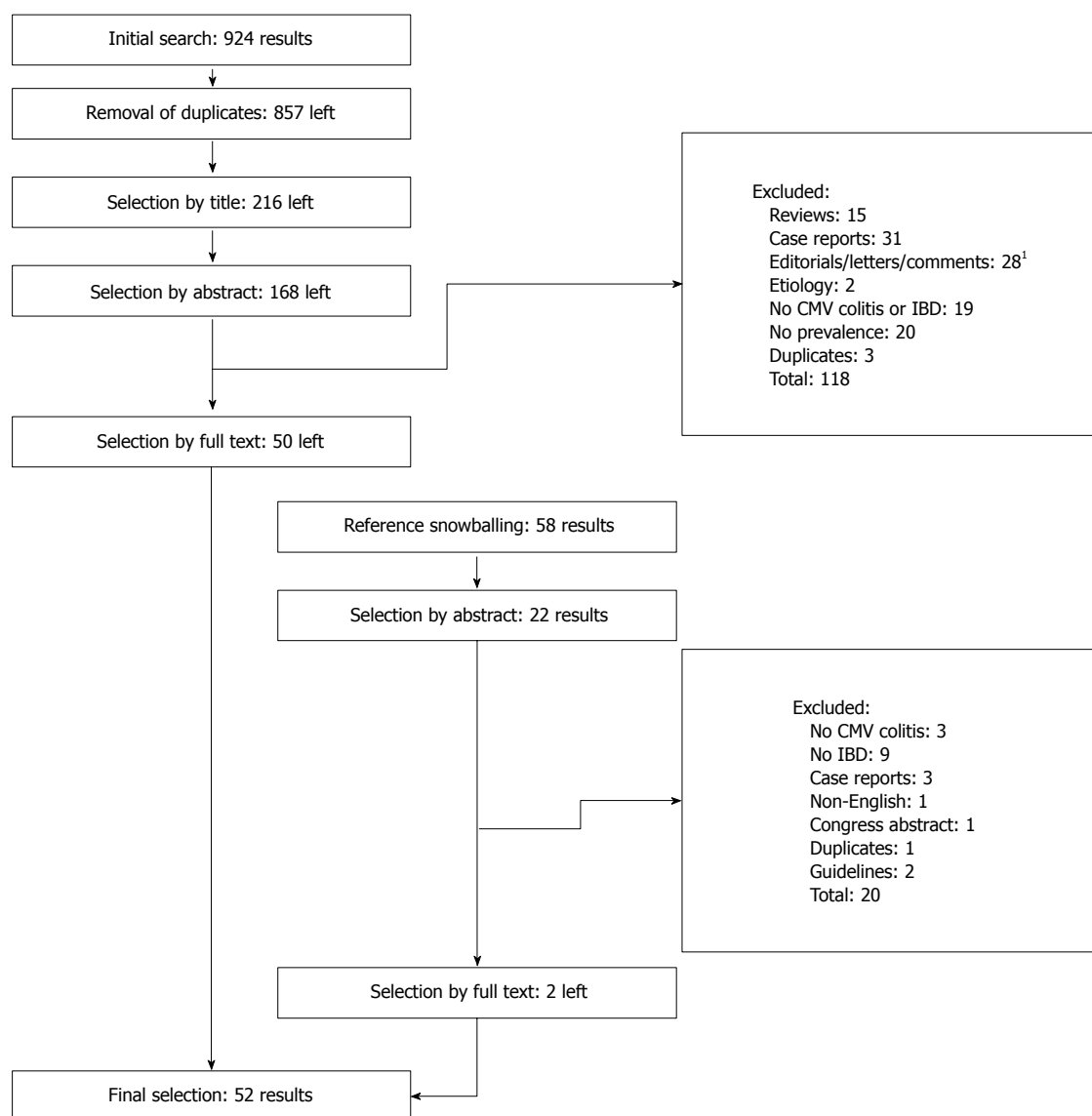
By using the authors' definition of either CMV infection or intestinal disease, we found different prevalence numbers in various regions of the world and in different subpopulations, which are depicted in scatterplots for CMV infection in Figures 4 and 5. If available CMV seroprevalence data are depicted in Figure 6. More detailed information on this topic and prevalence numbers for CMV intestinal disease are given in supplementary files (Appendix 2 A, B and Appendix 3 A, B). In general, the prevalence is negligible in healthy controls. We found a higher prevalence in UC than in CD both for CMV infection (median 14% vs 2.5%) and CMV intestinal disease (median 19.5% vs 11%). The prevalence is highest in steroid refractory disease for CMV infection (median 32.5%) and intestinal disease (median 32.5%).

### Diagnostic tests for CMV

More than 10 different tests were used to diagnose CMV (active) infection and intestinal disease, which can be found in the definition Tables 2 and 3. Histology, with or without immunohistochemistry (IHC), is most widely used to diagnose CMV disease (infection and/or intestinal disease;  $n = 30/48$ ). PCR on tissue is used in almost one third of the included studies (14/48). In Table 5 we present an overview of the test characteristics as described earlier in literature<sup>[24,63-70]</sup>.

## DISCUSSION

This systematic review maps the prevalence of both CMV infection and intestinal disease in IBD patients. We found that the prevalence greatly depends on the used definition. Studies reporting the highest prevalence of CMV infection use positive serum PCR as test, while studies that use positive antigenemia follow suit. In case of diagnosing CMV intestinal disease, the highest prevalence applies for tissue PCR ( $> 10$  copies/mg tissue). IBD patients with steroid refractory disease and those coming from East Asia have the highest prevalence of CMV infection and/or intestinal disease. In general CMV infection or intestinal disease is seen more frequently in UC compared to CD.



**Figure 1 Algorithm of inclusion.** <sup>1</sup>Letters/comments presenting original data were included in the review.

The difference of CMV infection and clinically relevant intestinal disease has been outlined earlier in literature. There, CMV infection is described as (incidental) finding of positive PCR or detection of CMV antigens or antibodies in serum, whereas CMV disease is a clinical syndrome where CMV infection is accompanied by manifest clinical symptoms<sup>[67,69,71,72]</sup>. Subclinical reactivation of CMV, without symptoms, is seen in approximately 50% of active UC cases on immunosuppressive therapy<sup>[62]</sup>. In practice however, the different entities described above, are used interchangeably. Likewise, no unified definitions have been used in clinical trials, and our study documents that the terms CMV infection and CMV intestinal disease are used reciprocally. This makes it difficult to compare data from different studies and to draw conclusions for outcome.

Interestingly, by using the author's definition, we found the highest prevalence of CMV infection and intestinal disease in East Asia. Population based CMV

seroprevalence studies are lacking, but a review on this topic found that seroprevalence tended to be highest in South America, Africa and Asia, and was also higher in parts of Europe and the Middle East<sup>[6]</sup>. The most likely explanation is the use of different diagnostic methods for CMV infection in different regions of the world. We show high prevalence numbers for CMV infection when antigenemia is used as test (Table 2), where 80% of these studies appear to come from Japan. CMV infection and more importantly CMV colitis is unusual in the healthy population<sup>[13,28,29,54]</sup> as described before in a systematic review<sup>[71]</sup>. Only one study reported presence of CMV DNA in 29% of asymptomatic control samples, but robust replication studies to confirm this unusual finding are lacking<sup>[14]</sup>. We found lower prevalence of CMV infection (and to a lesser extent in intestinal disease) for CD compared to UC<sup>[13,34]</sup> (Appendix 3). The most frequently studied population in relation to CMV is those with steroid resistant IBD or refractory UC. Apropos it should be

**Table 2 Prevalence by definition of cytomegalovirus-infection**

Definition	Studies, <i>n</i>	Median	Range
Antigenemia <sup>[17-21]</sup>	5	32%	6%-34%
Tissue PCR <sup>[22-25]</sup>	4	11%	1%-32%
IHC <sup>[26-29]</sup>	4	13%	9%-23%
HE <sup>[30-32]</sup>	3	17%	5%-36%
HE or IHC <sup>[33,34]</sup>	2	8%	5%-11%
HE and IHC <sup>[35, 36]</sup>	2	19%	12%-27%
IgM or HE or IHC <sup>[37,38]</sup>	2	9%	5%-13%
Antigenemia or Tissue PCR <sup>[39]</sup>	1	NA	NA
Serum PCR <sup>[40]</sup>	1	84%	-
(HE and IHC) or tissue PCR <sup>[41]</sup>	1	4%	-
Tissue PCR 10 copies/μg; OR histology OR Antigenemia <sup>[42]</sup>	1	54%	-
Antigenemia (2 tests: C7-HRP OR C10/C11) OR histology <sup>[43]</sup>	1	9%	-
Antigenemia or blood PCR <sup>quantitative</sup> <sup>[44]</sup>	1	36%	-
IgM or serum PCR or HE <sup>[45]</sup>	1	78%	-
IgM or tissue PCR <sup>qualitative</sup> or HE <sup>[46]</sup>	1	16%	-
IgG and (blood culture, antigenemia or histology or IgM or urine culture) <sup>[47]</sup>	1	6%	-
IgM or serum PCR <sup>qualitative</sup> or feces PCR <sup>[48]</sup>	1	5%	-
Inclusions: HE <sup>[49]</sup>	1	13%	-
Active infection: tissue PCR <sup>[50]</sup>	1	13%	-
Active replication: (HE or IHC) and antigenemia <sup>[51]</sup>	1	36%	-
Blood dissemination: (viremia, antigenemia, RNAemia) or (viremia or tissue culture) <sup>[52]</sup>	1	16%	-
Total: 21	Total: 36		

<sup>1</sup>One study defined a clinically relevant infection as > 10 IHC + cells/section but also recognized “scattered” positivity as 1-9 cells per section<sup>[29]</sup>; <sup>2</sup>Once mentioned as “acute infection”. PCR: Polymerase chain reaction; HE: Hematoxylin and eosin staining; IHC: Immunohistochemistry; IgM: Immunoglobulin M; IgG: immunoglobulin G; NA: Not applicable.

**Table 3 Prevalence by definition of cytomegalovirus-intestinal disease**

Definition	Studies, <i>n</i>	Median	Range
HE or IHC <sup>[1,2,38,44,53,54]</sup>	4	6%	2%-29%
HE <sup>[20,55]</sup>	2	9%	0%-17%
Tissue PCR <sup>quantitative</sup> > 10 copies/mg <sup>[56, 57]</sup>	2	34%	30%-38%
Serology and (IHC or antigenemia or serum PCR or tissue PCR) <sup>[58]</sup>	1	6%	-
IHC <sup>[59]</sup>	1	0%	-
HE or IHC or tissue PCR <sup>[51]</sup>	1	33%	-
(Pp65 antigenemia or tissue PCR <sup>quantitative</sup> ) and IHC and intestinal symptoms <sup>[39]</sup>	1	NA <sup>3</sup>	-
IHC positive when inflammation present <sup>[52]</sup>	1	1%	-
Total: 8	Total: 13		

<sup>1</sup>One study tested both before and after iv-steroid administration; <sup>2</sup>No data on prevalence: definition is used as the gold standard to compare other diagnostics; <sup>3</sup>No prevalence is reported in this study. PCR: Polymerase chain reaction; HE: Hematoxylin and eosin staining; IHC: Immunohistochemistry.

**Table 4 Prevalence by definition of cytomegalovirus-reactivation**

Definition	Studies, <i>n</i>	Median	Range
IgM or HE or PCR <sup>[160]</sup>	1	10%	-
Serum PCR in IgG positive patients <sup>[61]</sup>	1	0%	-
Antigenemia or plasma PCR <sup>[62]</sup>	1	36%	-
Total: 3	Total: 3		

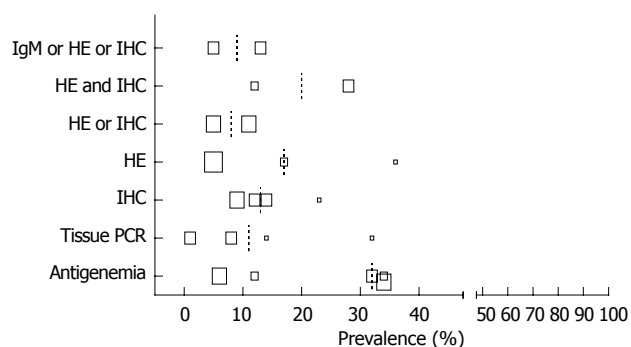
<sup>1</sup>Not specified what material is used for PCR testing. PCR: Polymerase chain reaction; HE: Hematoxylin and eosin staining; IgM: Immunoglobulin M; IgG: Immunoglobulin G.

noted that these studies use different definitions for steroid resistant IBD or refractory UC which may affect the prevalence<sup>[71,73]</sup>. We found the highest prevalence of CMV infection and CMV intestinal disease in steroid

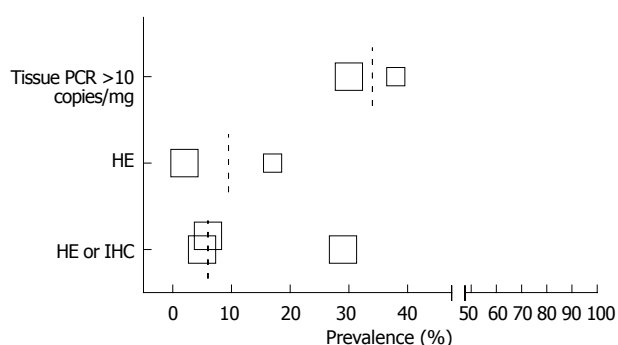
refractory disease, for each definition of CMV used<sup>[54]</sup> (Appendix 3). Whether or not CMV reactivation has a role in the process of steroid resistance, is still under debate<sup>[57,73-75]</sup>.

The surveyed literature contains 29 different methods to diagnose CMV infection and/or intestinal disease, probably mainly caused by the fact that still no single gold standard exists for (clinically relevant) CMV infection in IBD. In general, the literature recommends to process biopsies for HE and IHC<sup>[33,63,71,76]</sup> and/or if available by CMV DNA real-time PCR, with a cut off value that is yet to be identified<sup>[76]</sup>. The recent ECCO guideline<sup>[72]</sup> mentions that different techniques for diagnosis of CMV infection are available, but stops short of defining a gold standard. The guideline refers to histopathology combined with IHC (using monoclonal antibodies) as highly specific and sensitive

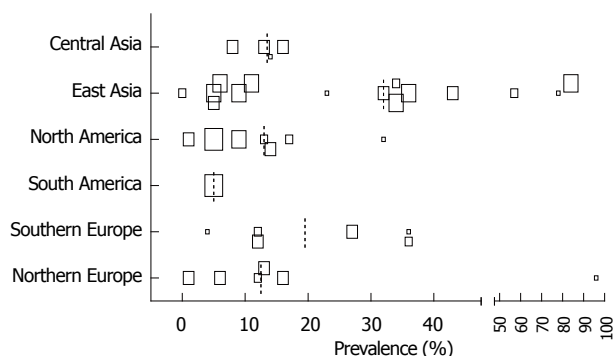




**Figure 2** Prevalence cytomegalovirus infection by authors definition. Size of the squares corresponds with the population size in 5 categories ( $n = 0-25$ ,  $n = 25-50$ ,  $n = 50-100$ ,  $n = 100-250$ ,  $n > 250$ ). Median depicted as dotted line.

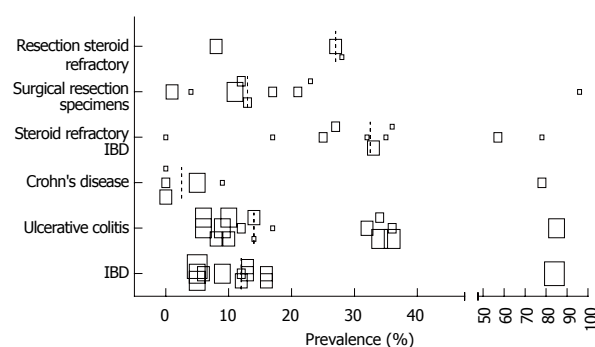


**Figure 3** Prevalence cytomegalovirus intestinal disease by authors definition. Size of the squares corresponds with the population size in 5 categories ( $n = 0-25$ ,  $n = 25-50$ ,  $n = 50-100$ ,  $n = 100-250$ ,  $n > 250$ ). Median depicted as dotted line.

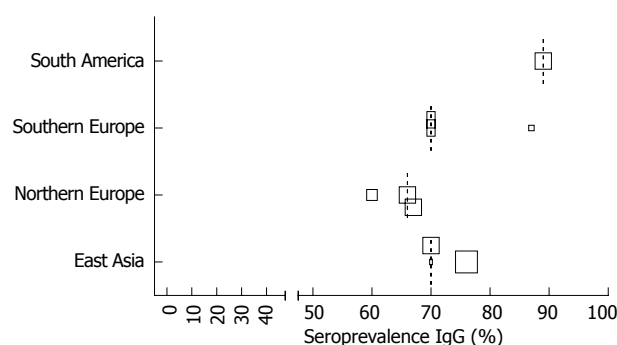


**Figure 4** Prevalence cytomegalovirus infection in different global regions by authors definition. Size of the squares corresponds with the population size in 5 categories ( $n = 0-25$ ,  $n = 25-50$ ,  $n = 50-100$ ,  $n = 100-250$ ,  $n > 250$ ). Median depicted as dotted line.

for verifying CMV infection in tissue. In addition the guideline describes quantitative PCR in tissue and in blood as the most commonly used and advantageous technique for diagnosis of CMV infection. Quantitative PCR has a low sensitivity for diagnosing CMV colitis in patients with moderate to severe UC, and cannot substitute histopathology diagnosis<sup>[44]</sup>. Already in the nineties consensus meetings were held to formulate the definition for CMV infection in general and for all organ specific involvements in transplant recipients.



**Figure 5** Prevalence cytomegalovirus infection in different sub populations, by authors definition. Size of the squares corresponds with the population size in 5 categories ( $n = 0-25$ ,  $n = 25-50$ ,  $n = 50-100$ ,  $n = 100-250$ ,  $n > 250$ ). Median depicted as dotted line.



**Figure 6** Cytomegalovirus seroprevalence data in different regions of the world. Size of the squares corresponds with the population size in 5 categories ( $n = 0-25$ ,  $n = 25-50$ ,  $n = 50-100$ ,  $n = 100-250$ ,  $n > 250$ ). Median depicted as dotted line.

These definitions were updated again in 2002<sup>[67]</sup>. CMV infection was defined as isolation of the CMV virus or detection of viral proteins or nucleic acid in any body fluid or tissue specimen. There CMV (gastro)intestinal disease was defined by identification of a combination of (1) clinical symptoms; (2) findings of macroscopic mucosal lesions on endoscopy; and (3) demonstration of CMV infection (by culture, histopathology, IHC, or in situ hybridization) in a (gastro)intestinal tract biopsy specimen. According to this guideline detection of CMV by PCR alone is insufficient for diagnosis of CMV gastrointestinal disease. Applying these criteria to IBD patients can be more complicated, since ulceration can also be caused by the underlying IBD. Since then, multiple more sensitive diagnostic tests have been developed to detect CMV, but a threshold or definition of clinical relevant CMV infection or intestinal disease remains to be established. We suggest that a global multidisciplinary consensus meeting on CMV and IBD should be held, in order to develop one unified definition of clinically relevant CMV intestinal disease. In this context, clinically relevant describes the situation that symptoms appear, clinical deterioration occurs, and (antiviral) treatment should be initiated. This single definition could be used in clinical practice, but also in future trials, to serve as a gold standard in the discussion on outcome and optimal (antiviral)

**Table 5** Test characteristics different diagnostic tools for cytomegalovirus

Test	Pro	Con	Sens	Spec
Serology	Fast, quantification possible	Systemic, not proving intestinal disease;	98%-100%	96%-99%
Antigenemia	Fast, quantification possible	Systemic, not proving intestinal disease labor intensive	60%-100%	83%-100%
Serum PCR	Fast, quantification possible	Systemic, not proving intestinal disease	65%-100%	40%-94%
HE Histology (gold standard?)	Specific, proofs intestinal disease	Slow; low sensitivity	10%-87%	92%-100%
Histology with IHC	Specific, proofs intestinal disease	Slow	93%	92%-100%
Tissue PCR	Quantification possible	Cut-off point unclear, uncertain clinical significance	65%-100%	40%-100%
Stool PCR	Quantification possible	Little experience	83%	93%
Viral Culture	Very specific	Very slow	45%-78%	89%-100%
Rapid Vial culture	Very specific	Little experience	68%-100%	89%-100%

Sens: Sensitivity; Spec: Specificity; PCR: Polymerase chain reaction; HE: Hematoxylin and eosin staining; IHC: Immunohistochemistry.

treatment of CMV in IBD patients.

Our study has several strengths. First of all, we show that the use of different definitions of CMV infection impacts reported prevalence rates. Second, we provide CMV prevalence data for several important sub populations, as UC, CD, steroid refractory disease, and patients in different continents of the world. Third, two independent reviewers reviewed all eligible studies, and three reviewers read all full text papers, with good agreement scores based on the presented kappa value. Our study comes with some limitations. None of the included studies were randomized, most of them had a retrospective design and only some used blinding of endoscopists or pathologists. The heterogeneity of the design of included studies and wide variations in used definitions for both CMV infection and intestinal disease made it impossible to perform a meta-analysis on these data.

In conclusion we find a wide variety in definitions used for CMV infection and intestinal disease in IBD patients, which impacts corresponding prevalence rates and eventually the outcome in different trials. A global consensus meeting is pivotal to develop one unified gold standard definition for clinically relevant CMV, to be used in clinical practice as well as in future trials.

## COMMENTS

### Background

Cytomegalo virus (CMV) infection is common, but mostly asymptomatic in the general population. In immunocompromised patients CMV infection may result in complications and organ-specific disease such as colitis. The exact role of CMV in clinical deterioration in inflammatory bowel disease (IBD) patients under debate. There is no global consensus on definitions of clinically relevant CMV disease in IBD patients.

### Research frontiers

The optimal treatment strategy of refractory IBD, involving CMV infection, remains to be determined. Various treatment options, as the use of antiretroviral agents or intensified immunosuppressive therapy are being studied. It is most likely that the outcomes of the different trials will be influenced by the used definition of CMV infection and intestinal disease. Therefore one unified definition is essential.

### Innovations and breakthroughs

Multiple diagnostic tests circulate to diagnose CMV infection. As a result, more

than 20 definitions are used in clinical practice and for research purposes. This review is the first to address this challenging issue and the problems resulting from like the interpretation of study outcomes on this topic.

### Applications

A global consensus meeting is necessary to determine one unified definition for CMV infection and intestinal disease in IBD to be used in clinical practice and future research.

### Terminology

CMV-infection: systemic presence of viral antigens or replication markers. CMV-intestinal disease: evidence of viral presence in intestinal tissue. Steroid refractory disease: IBD not responding to treatment with high dose intravenous corticosteroids.

### Peer-review

This is an interesting and timely manuscript addressing a significant discrepancy between the different definitions of CMV disease in IBD.

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